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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/745,920	12/21/2000	Kenneth C. Parker	SYP-155 7783/571	2871

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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/745,920	PARKER, KENNETH C.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/6/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-24 and 26-33* is/are pending in the application.

4a) Of the above claim(s) *30-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-24 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-7,9-24 and 26-33* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3 pages*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and remarks, filed 10/6/04, are acknowledged. Amended claims 1, 9, 17, 18, 19, 23, and 26 as well as canceled claims 8 and 25 are acknowledged.

Applicant's arguments, filed 10/6/04, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-7, 9-24, and 26-29 are herein under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-24, and 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 (line 16) and 23 (line 16) recite the limitation "the biological fragment" in 16. There is insufficient antecedent basis for this limitation in the claim because such a fragment may indicate a known biomolecule fragment, or confusingly, a biological fragment of the sample biomolecules. Claims 2-7, 9-22, 24, and 26-29 are also rejected

due to their direct or indirect dependency from claims 1 and 23. This rejection is necessitated by amendment.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-7, 11-17, 21-24, and 28-29 is maintained under 35 U.S.C. 103(a) as being unpatentable over Yates, III et al. (P/N 6,017,693), in view of Gras et al. (Electrophoresis 1999, Volume 20) and Wright et al. (P/N 5,710,713). This rejection is maintained and reiterated for reasons of record.

Yates, III et al. describe a method of using tandem mass spectrometry to determine sequences that are likely to be identical to an experimentally derived peptide (col. 2, lines 22-27). Yates, III et al. describe introducing an unknown peptide into a first mass spectrometer to separate it from the rest of the sample (col. 2, lines 54-64). The peptide and its fragments are then passed through a second mass spectrometer to obtain an intensity and mass-to-charge ratio (m/z) (col. 3, lines 4-7), which includes measuring mass signals and a mass spectrum of a biomolecule fragment as seen in Figure 5 (col. 3,

lines 7-9). Yates, III et al. describe a method in Figure 2 where an unknown (12) is analyzed in a tandem mass spectrometer (14) to obtain fragment spectrum (16) and compared (24) to the mass spectra (22) of proteins from a protein sequence library (20) on a computer. Yates, III et al. describe performing this comparison and calculating a closeness-of-fit measure or score for each of a plurality of mass spectra (col. 4, lines 9-16). Yates, III et al. describe determining if a fragment mass is found in a measured fragment spectrum and scores are generated and sorted in a repeated cycle which results in one or more candidate amino acid sequences (col. 3, lines 21-28). Yates, III et al. describe high-scoring candidate sequences (col. 3, lines 29-30). Yates, III et al. describe a mass tolerance of the unknown peptide from which spectra from known sequences (i.e. potential source biomolecules) are identified if they fall within this tolerance amount (col. 4, lines 59-67 and Figure 4) which is reasonably interpreted as the biomolecule fragment detection parameter. Yates, III et al. describe an example using a tolerance of +0.05% of the mass of the unknown peptide used (col. 5, lines 25-26) which is reasonably interpreted as a detection efficiency as stated in claims 7 and 24. Yates, III et al. describe the high probability or likelihood that the unknown peptide has an identical amino acid sequence to one of the subsequences taken from the protein sequence library due to the high closeness-of-fit score with respect to the spectra comparison (col. 4, lines 16-23). Yates, III et al. further describe the high probability of the unknown protein and the known protein from the library as being identical or similar with subsequences with high closeness-of-fit scores (col. 4, lines 23-29). Yates, III et al. describe performing further MS-MS analysis if original scoring procedures do not delineate an answer of protein match (col. 8, lines 53-61) as stated in claim 23.

Yates, III et al. describe the calculation of closeness-of-fit (56) in Figure 3 and then the selection of sequences with the highest scores (58). Yates, III et al. describe outputting matching data for sequences with the highest correlation function (62).

Yates, III et al. describe normalizing the spectrum (col. 4, lines 35-38) which is reasonably interpreted as a form of calibration as in instant claim 4.
Yates, III et al. describe the above-mentioned procedure as being performed automatically on a computer (col. 4, lines 30-34). Yates, III et al. describe computational resources and storage facilities (col. 9, lines 24-49 and col. 21, lines 8-10) as stated in claims 28 and 29. Yates, III et al. describe identifying 200 of the most intense ions from the experimentally-derived fragment spectrum (col. 4, lines 44-45) as mentioned in claim 14. Yates, III et al. describe the calculation of closeness-of-fit (56) in Figure 3 and then the selection of sequences with the highest scores (58). Yates, III et al. describe outputting matching data for sequences with the highest correlation function (62) which suggests that any scores lower than the highest scores are likely absent and therefore are not outputted (also see Figure 6D) as stated in claim 2. Yates, III et al. do not teach correcting a mass intensity for an isotopic variant (claim 3), removing noise (claim 5), removing artificial background intensity (claim 6), weighted biomolecule scores, fragment counts, and signal intensity scores to determine the likelihood of the presence or absence of a biomolecule as well as determining a relative concentration based on the biomolecule score.

Gras et al. describe a program that identifies a protein based on mass spectra despite chemical modifications (abstract, lines 1-5) which could be an isotopic variant as stated in claim 3. Gras et al. also describe this determination of isotopic variants via

software that often comes with the spectrometer (page 3538, col. 1, lines 1-5 and col. 1, third paragraph). Gras et al. describe a trend or baseline as the signal produced if no material entered the mass spectrometer and in the absence of noise (page 3537, col. 2, lines 10-14; page 3538, col. 1, lines 18-24; and Figure 1) which is reasonably interpreted as the removal of noise and background intensity as stated in claims 5 and 6. Gras et al. describe the smoothing out of error functions related to the mass signals (page 3538, lines 21-26). Gras et al. describe using selected parameters to search proteins in a database that match the experimental spectra and assigning a score to the candidate protein (page 3541, col. 1, paragraph 2). Gras et al. describe the parameters' effects on the quality and efficiency of the identification (page 3541, col. 1, paragraph 3) as mentioned in claims 7 and 24. Gras et al. describe parameters that include the maximum distance between experimental and theoretical masses, the minimum number (or score) of matched peptides necessary for a protein to be selected, and the number of peaks returned by the peak detection program (page 3541, col. 1, paragraph 4). Gras et al. describe eliminating the least likely proteins in the list of candidates using parameters such as the minimum number of matched peptides or number of detected peaks, as well as depending on their thresholds (page 3541, col. 2, paragraph 1). Gras et al. describe the parameter of peak intensity in the mass spectrum as well (page 3542, col. 2, lines 40-44). Gras et al. describe a mass level parameter that characterizes the degree of match between the experimental mass and the peptide mass of the search library protein (page 3541, col. 1, paragraph 3) that is reasonably interpreted as a mass error. Gras et al. describe defining score calculations by determining the most important parameters, their relative weights and how to integrate them all into the score calculation (page 3542, col. 2, lines 20-23).

Gras et al. describe counting the number of experimental masses matching theoretical peptide masses (page 3542, col. 2, lines 29-33) which are fragment counts. Gras et al. describe the concept of the more identified masses a protein has in the mass spectrum, the higher is the confidence for its identification (page 3542, col. 2, lines 33-35). Gras et al. describe assigning weights to each peptide mass, depending on the presence of a match resulting in a score calculation (page 3542, col. 2, lines 36-41 and page 3543, col. 2, lines 15-19). Gras et al. describe taking into account the calibration error of the measuring device, eliminating masses that are too far from the regression line, and repeating this process when the previous no masses were eliminated in the previous step (page 3543, col. 1, paragraph 3). Gras et al. describe identifying proteins via scores obtained of the proteins in a ranked list of candidate proteins (page 3543, col. 2, lines 37-41).

Wright et al. describe the concentration in the mass spectrometer, its use in standardization of the process including relative estimates, and relative errors resulting without a calibration correction (col. 17, lines 6-26) as stated in claim 16.

Yates, III et al. state that interpretation of the fragment spectra so as to produce candidate amino acid sequences is time-consuming, often inaccurate, and highly technical (col. 1, lines 52-59). Yates, III et al. note that relying on human interpretation often means that analysis is relatively slow and lacks strict objectivity (col. 1, lines 59-60). They further state that approaches based on peptide mass mapping are limited to peptide masses derived from an intact homogeneous protein generated by specific and known proteolytic cleavage (col. 1, lines 61-64). Yates, III et al. state that it would be useful to provide a system for correlating fragment spectra with known protein sequences in a fast and objective way (col. 1, lines 65-67). Yates, III et al. invented a spectral interpreting

method that could be used with any size peptide (col. 20, lines 59-60). However, Yates, III et al. note that certain variations and modifications could be made to their invention. One of ordinary skill in the art would have been motivated to make further improvements to the identification method of spectral data, such as that stated by Yates, III et al. (col. 2, lines 5-27) in order to provide more accurate results as stated by Yates, III et al. (col. 1, lines 52-59). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include features such as correcting a mass intensity for an isotopic variant, removing noise and artificial background intensity, creating weighted biomolecule scores, fragment counts, and signal intensity scores to determine the likelihood of the presence or absence of a biomolecule, as stated by Gras et al., as well as determining a relative concentration based on the biomolecule score, as stated by Wright et al., in order to provide precise and fast determination of peptide masses, even if the peaks are of low intensity and overlap (Gras et al., abstract, lines 6-7) and to provide accurate and precise concentration estimates (Wright et al., col. 17, lines 19-21) to create more accurate results in mass spectral identification, as stated by Yates, III et al. (col. 1, lines 52-59).

Thus, Yates, III et al., in view of Gras et al. and Wright et al. motivate the limitations of claims 1-7, 11-17, 21-24, and 28-29.

Applicant states neither prior art reference teaches or suggests "determining a biomolecule fragment score", using "the mass signal intensity for said mass signal, a biomolecule fragment detection parameter... and a mass error for said mass signal". The Applicant has not argued the 103 rejection beyond the argument regarding these phrases.

These limitations along with the amended limitations are described above and Applicant has failed to provide evidence suggesting why the interpretations of the prior art references would be considered improper. Applicant states material from claims 8 and 25 were not rejected and were placed in the dependent claims 1 and 23. While some of the claim limitations of cancelled claims 8 and 25 have been amended into claims 1 and 23, not all of the limitations of cancelled claims 8 and 25 (i.e. separate determining steps) have been amended into claims 1 and 23. For example, original (and now canceled) claims 8 and 25 had specific determination steps whereas the amendments of claims 1 and 23 only list the amended portions from claim 8 regarding elements of a function. Elements of the recited "function" of claims 1 and 23 (line 10 of each) were previously discussed in the prior art rejection of the previous office action, mailed 1/12/04. Therefore, the 35 USC 103(a) rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

Ardin H. Marschel 12/15/04
ARDIN H. MARSCHEL
PRIMARY EXAMINER

December 15, 2004